REMARKS

Claim Status

Claims 1-6 are currently pending. Claims 3-6 have been withdrawn from consideration. No amendments have been made herein to the pending claims.

35 U.S.C. § 103(a) Rejection

The Office rejected claims 1 and 2 under 35 U.S.C. § 103(a) as allegedly obvious over Puurunen, K. et al., "An α_2-adrenergic antagonist, atipamezole, facilitates behavioral recovery after focal cerebral ischemia in rats," *Neuropharmacology* (2001) 40:597-606 ("Puurunen") in view of Ginsberg, M.D. and Busto, R., "Rodent models of cerebral ischemia," *Stroke* (1989) 20:1627-1642 ("Ginsburg") and Leker, R.R. and Neufeld, M.Y., "Anti-epileptic drugs as possible neuroprotectants in cerebral ischemia," *Brain Res. Rev.* (2003) 42:187-203 ("Leker"). Final Office Action at 3.

Applicants respectfully disagree with and traverse this rejection.

The Office withdrew its anticipation rejection over Puurunen, apparently conceding that Puurunen does not expressly or inherently disclose a method according to the instant claims. In particular, the Office concedes that "Puurunen does not teach the administration of the drug to human patient at risk of developing epilepsy." However, the Office relies on Ginsberg for its teaching that rat models are appropriate models for ischemic brain injury and on Leker "to demonstrate that cerebral ischemia leads to epileptic attack." Office Action at 4-5. The Office concludes that "when a patient with brain ischemia is treated with atipamezole, **the compound will inherently inhibit the development of epilepsy upon administration**." Office Action at 5 (emphasis added).

However, obviousness cannot be predicated on what was not known at the time an invention is made, even if the inherency of a certain feature can be later established. *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993); *see also* M.P.E.P. 2141.02. Furthermore, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily*** present in the thing described in the reference.... Inherency, however, ***may not be established by probabilities or possibilities***. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, (Fed. Cir. 1999) (emphasis added). *See also* M.P.E.P. §2112.

Here, in fact, the Office acknowledges that "Leker et al teaches that epileptic seizures ***may*** be the result of cerebral ischemia and ***may*** also cause brain damage." Office Action at 5 (emphasis added). That teaching does not rise to the requisite level of necessarily and inevitably, as discussed above. Thus, the Office's conclusion that administering atipamezole to a stroke patient will necessarily and inevitably lead to the claimed methods is unsupported by the disclosure of the cited art.

The Office has failed to establish a *prima facie* case of obviousness for at least the additional reason that Applicants have proceeded contrary to the conventional wisdom at the time of the invention, evincing the non-obviousness of the instant claims. M.P.E.P. § 2145. ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." (citing *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)).

At the time of invention, the art actually taught away from using alpha2-adrenoceptor antagonists to inhibit the development of epilepsy, as presently claimed.

Specifically, it was known in the art that psychostimulants caused seizures (Bowyer, J.F. et al., "Brain Region-Specific Neurodegenerative Profiles Showing The Relative Importance Of Amphetamine Dose, Hyperthermia, Seizures, And The Blood-Brain Barrier," *Ann. NY Acad. Sci.* (2008) 1139:127-39) while at the same time being useful for enhancing recovery after brain trauma, such as ischemia (Martinsson, L. and Eksborg, S., "Drugs For Stroke Recovery: The Example Of Amphetamines," *Drugs Aging* (2004) 21(2):67-79). Consequently, a skilled artisan would have expected psychostimulants to be neuroprotective, but also to potentially cause or stimulate epileptic convulsions.

Atipamezole, an alpha2-adrenoceptor antagonist that stimulates central noradrenaline release, had been reported to potentiate kainic acid induced convulsion and mortality in rats. (Halonen, T. et al., "α2-Adrenoceptor Agonist, Dexmedetomidine, Protects Against Kainic Acid-Induced Convulsions And Neuronal Damage," *Brain Res.* (1995) 693:217-24). Aware of atipamezole's epileptogenesis qualities, analogous to other psychostimulants, the researchers of Puurunen were not attempting to prevent epilepsy but instead were simply attempting to determine whether atipamezole behaves like other psychostimulants after ischemia, i.e., offering neuroprotective effects.

Furthermore, other non-specific alpha2-adrenoceptor antagonists, such as idazoxan and yohimbine were known to facilitate epileptogenesis, i.e., to cause epilepsy. (Gellman R. L. et al, "Alpha-2 receptors mediate an endogenous noradrenergic suppression of kindling development," *J. Pharmacol. Exp. Ther.* (1987) 241(3):891-8.). As a result, the skilled artisan would not have been motivated to use alpha2-adrenoceptor antagonists, known to be psychostimulants and actually

epileptogenic agents, to inhibit epilepsy. Therefore, because Applicants proceeded directly contrary to this accepted wisdom, a *prima facie* case of obviousness has not been established, and this rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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